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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,823	03/14/2005	Kazuhisa Sugimura	SUGIMURA5	4585

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EXAMINER	
CROWDER, CHUN	
ART UNIT	**PAPER NUMBER**
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,823	SUGIMURA ET AL.	
	Examiner	Art Unit	
	Chun Crowder	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/20/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *14-17 and 30-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 18-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/14/2005 and 05/09/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group I (drawn to a gene fragment encoding for a human anti-human monocyte chemoattractant protein-1 (MCP-1) and species of fragments without one or several amino acids deleted, substituted or added, filed 12/20/2006, is acknowledged.

Upon further consideration and in the interest of compact prosecution, the prior art search has been extended to include all species of the gene fragment including fragments with one or several amino acids are deleted, substituted or added.

Claims 1-53 are pending.

Claims 14-17 and 30-53 have been withdrawn from further consideration by the Examiner under 37 C.F.R. 1.142(b), as being drawn to nonelected inventions.

Claims 1-13 and 18-29 are currently under consideration as they read one the elected invention of a gene fragment encoding for a human anti-human MCP-1 antibody.

2. Applicant's IDSs, filed 06/14/2005 and 05/09/2006, are acknowledged and have been considered except for references AB (JP 09-67399A), AC (JP 2002-297098A) and AD (WO01/89582A1) for which have only been considered to the extent of the English translations of the abstracts.

3. Claims 13, 20, 23, 26, and 29 are objected to for following reasons:

A) Claim 13 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim 9.

Claim 13 fail to further limit the subject matter of the previous claim 9. Claim 9 encompasses a gene fragment coding a scFv of a human nati-MCP-1 antibody "consisting of" a gene fragment coding for a VH chain and a gene fragment coding for a VL chain, while the dependent claim 13 is drawn to a gene fragment consisting of the scFv gene of claim 9 combined with either a portion of a human antibody CH gene or with a portion of a CL gene; as such claim 13 does not limit the subject matter of the previous claim 9.

Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form.

B) Claims 20, 23, 26 and 29 are objected to for following informalities:

Claims 20, 23, 26 and 29 recite "CH chain has the amino acid sequence depicted in SEQ ID NO:2". It appears that the "CH" is a typographic error because the instant SEQ ID NO:2 is the VH chain (e.g. see claim 3), not the CH chain.

Appropriate correction is required.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-13 and 18-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-13 and 18-29 are drawn to a gene fragment coding for VH chain and/or VL chain of a human anti-human MCP-1 antibody.

According to Genes IV (Lewin et al, Oxford University Press, 1990. right column on page 810), a gene is defined as "the segment of DNA involved in producing a polypeptide chain; it includes regions preceding and following the coding regions (leader and trailer) as well as intervening sequences (introns) between individual coding segments (exons)." From the teachings of the specification, however, the nucleic acid sequences coding VH chain and VL chain of an human anti-MCP-1 antibody appear limited to the specific coding regions (e.g. mRNA, see pages 8-9 of the instant specification), and do not include expression control elements that fall under the definition of a gene. Accordingly, the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

B) Claims 1-13 and 18-29 are indefinite in the recitation of "the biological activity" because the metes and bounds of the biological activity is not clear and is ambiguous. For example, page 14 of the instant specification discloses certain "biological activity" of the human anti-MCP-1 antibody encoded by the claimed gene; however, it is unclear as to which "biological activity" or the requisite structural/functional characteristic is/are intended or encompassed by the human anti-MCP-1 antibody coded by the claimed gene.

It is suggested to amend the claims to recite the "the biological activity" encompassed by the human anti-human MCP-1 antibody coded by the claimed gene fragment.

C) Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06.

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 1-13 and 18-29 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-13 and 18-29 are drawn to a gene fragment coding for a human anti-human MCP-1 antibody.

Claims 1-13 and 18-29, as written, do not sufficiently distinguish over antibodies as they exist naturally, e.g autoantibodies against human MCP-1, because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980).

The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" or "purified" as disclosed on pages 9-10 of the instant specification. See MPEP 2105.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-13 and 18-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A) Claims 1-8 and 18-29 encompass the following recitation as part of the invention:

claims 1-4 recite "a gene fragment coding for a VH chain or a portion thereof of a human anti-human MCP-1 antibody",

claims 5-8 recite "a gene fragment coding for a VL chain or a portion thereof of a human anti-human MCP-1 antibody",

claims 3, 7, 19, 22, and 25 recite "one or several amino acids are deleted, substituted or added",

claims 18-29 encompass a gene fragment coding VH chain "and/or" a VL chain of an human anti-MCP-1 antibody, and

claims 1-8 and 18-29 further recite the functional limitation of the human anti-MCP-1 antibody "that binds to human MCP-1 and inhibits the biological activity".

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites.

For example, Li et al. (Biochemistry 2000. 39:6296-6309) in a study of three-dimensional structures of antigen-bound Fab from monoclonal antibody show that all six CDRs of the variable domains of the Fab are involved in binding of an antigen (see entire document, particularly page 6301).

Therefore, the claimed gene coding for a VH chain alone or a VL chain alone of the human anti-human MCP-1 antibody would not encompass the claimed the limitation of "binds to human MCP-1 and inhibits the biological activity".

The specification does not provide sufficient direction or guidance regarding how to match a gene fragment coding for a VH chain to any other VL chains to form a functional antibody as broadly defined by the claims, other than the claimed VH chain of SEQ ID NO:2 (encompassing CDR1, CDR2, and CDR3 of SEQ ID NOs: 3, 4, and 5, respectively) and the VL chain of SEQ ID NO:7 (encompassing CDR1, CDR2, and CDR3 of SEQ ID NOs: 8, 9, and 10, respectively).

Further, the state of the art acknowledges at the time the invention was made that even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 pages 1979-1983); Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function (see entire document, particularly page 1979).

It is unlikely that gene fragment coding for a portion of the VH chain or a portion of the VL chain or gene fragment coding for VH and/or VL with one or several amino acids are deleted, substituted or added as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an human anti-human MCP-1 antibody in unspecified order would have the required functions of binding to human MCP-1 and inhibiting the biological activity thereof.

The specification provides insufficient direction or guidance regarding how to made and use the gene fragments as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention

B) Claims 1-13 and 18-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a written description rejection.

The specification broadly describes and the claims encompass as part of the invention "a gene fragment" coding for a VH chain and/or VL chain of a human anti-human MCP-1 antibody.

The specification does not describe any "gene fragment" coding for a VH chain and/or VL chain of a human anti-human MCP-1 antibody.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. (See Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, especially page 1106 3rd column). A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. MPEP 2163 II.A.3a.ii.

The specification as-filed does not disclose a sufficient number of species to support the "gene fragment" as broadly encompassed by the claimed invention.

Rather, the instant specification appear to provide the written description of the DNAs encoding human VH and VL chains amplified from mRNAs extracted from peripheral blood B lymphocytes and screened using phage library for antibody that bind human anti-human MCP-1 (see pages 8-9 of the instant specification); and the instant specification does not appear to describe any "gene fragment" coding for the antibody.

In addition, the claimed gene fragment would encompass continuous or discontinuous regions of nucleic acids "coding for an human anti-human MCP-1 antibody". The claimed products may also contain additional coding and non-coding region. In addition, the invention could embrace any "one or several amino acids are deleted, substituted or added" coded by the nucleotides throughout the entire stretch of the gene and may result in an antibody that would not bind to human MCP-1 and inhibit the biological activity thereof.

For example, antibody diversity is critical and evident for a proper immune response, including making antibodies of interest. During B cell differentiation, antibody diversity is generated in the heavy and light chains of the immunoglobulin by mechanisms including multiple germ line variable (V) genes, recombination of V gene segments with joining (J) gene segments (V-J recombination) and recombination of V gene segments with D gene segments and J gene segments (V-D-J recombination) as well as recombinational inaccuracies. Furthermore, somatic point mutations that occur during the lifetime of the individual, immunized individual (e.g. immunized mouse for hybridomas) or a cell line also lead to antibody diversity. Thus, a huge number of different antibody genes coding for antibodies with exquisite specificity can be generated. The total potential immunoglobulin repertoire exceeds 10^{11} (Janeway et al. Immunobiology by Current Biology Ltd. 1990 Chapter 3, pages 3:1-3:38, see entire document, particularly page 3:12).

Therefore, given the well known polymorphism of immunoglobulins / antibodies; applicant was not in possession of the vast repertoire of "gene" coding for a VH chain and/or VL chain including portions thereof and one or several amino acids are deleted, substituted, or added, other than cDNAs that may be based upon the cDNAs corresponding to the particular human anti-human MCP-1 antibody.

Applicant was not in possession of the structural attributes of a representative number of species possessed by the members of the genus of "gene" coding for a VH chain and/or VL chain including portions thereof and one or several amino acids are deleted, substituted, or added, commensurate in scope with the claimed invention.

Such sequences do not meet the written description provision of 35 USC 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

The cDNAs coding for the claimed antibody as described by the instant application do meet the written description provision of 35 USC 112, first paragraph.

"Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997).

The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Id. 43 USPQ2d at 1406.

In the absence of disclosure of relevant, identifying characteristics of the "gene" coding for the claimed antibody, there is insufficient written disclosure under 35 U.S.C. 112, first paragraph.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 1115).

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1, 5, 9-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Hiestand et al. (WO 02/02640. Reference AW on IDS) (see entire document).

Hiestand et al. teach method of making human anti-human MCP-1 antibodies including single chain antibody and antigen-binding fragment of the antibody such as $F(ab')_2$ and Fab using recombinant techniques (see entire document, particularly 3rd paragraph on page 1, pages 3 and 7-8). Further, Hiestand et al. teach that genes encoding a VH domain and VL domain of the antibody can be cloned into expression vectors to produce the recombinant antibody (e.g. see pages 8-9). Furthermore, Hiestand et al. teach that said antibody is capable of binding to human MCP-1 (e.g. see page 14) and can inhibit the biological activities such as MCP-1 mediated signaling and binding of MCP-1 to its receptor (see pages 13 and 15-16, in particular).

Given that it is not clear what the claimed "biological activity thereof" of the human anti-human MCP-1 antibody encompasses (see discussion in Section 5B above) and the instant specification discloses the claimed antibody may interact with human MCP-1 and thereby inhibit the binding between human MCP-1 and its receptor (see Industrial Applicability on page 14 of the instant specification), the reference antibody capable of binding to human MCP-1 and inhibiting of binding of MCP-1 to its receptor and thereby inhibiting MCP-1 mediated signaling meets the claimed limitation.

Therefore, the reference teachings anticipate the claimed invention.

12. The following claimed subject matter appears to be free of the prior art :

human anti-human MCP-1 antibody consisting of:

a VH chain of SEQ ID NO:2 encompassing CDR1 of SEQ ID NO:3, CDR2 of SEQ ID NO:4, CDR3 of SEQ ID NO:5, and

.a VL chain of SEQ ID NO:7 encompassing CDR1 of SEQ ID NO:8, CDR2 of SEQ ID NO:9, CDR3 of SEQ ID NO:10

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chun Crowder whose telephone number is 571-272-8142. The examiner can normally be reached on 8:30-5:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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February 8, 2007

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2/26/07